1. (Amended) A vector that encodes a replication competent HIV-1 virus, said vector comprising an HIV-1 genome in which a region non-essential for viral replication has been replaced by a reporter gene, wherein said vector is suitable for use in a high volume anti-viral assay.

A1

2. (Amended) The vector according to claim 1, wherein said reporter gene is selected from the group consisting of the renilla luciferase reporter gene, the SEAP reporter gene and the green fluorescence protein gene.

13. (Amended) A vector that encodes a replication competent HIV-1 virus, said vector comprising an HIV-1 genome in which a region non-essential for viral replication has been replaced by a nucleic acid sequence encoding a functional renilla luciferase enzyme, wherein said vector is suitable for use in a high volume anti-viral assay.

A2

Remarks

Claims 1-23 are pending. Claims 1, 2 and 13 have been amended. Attached hereto is "Appendix A", entitled "Amended Claims With Markings to Show Changes Made".

Section 102 Rejections

The Examiner has rejected claims 1, 2, 4, 10 and 11 under 35 U.S.C. 102(b) as being anticipated by EP 361749 ("Haseltine"). This rejection is respectfully traversed.

The claimed invention is directed to a replication-competent HIV-1 reporter virus that allows rapid high volume screening of anti-viral compounds. The reporter virus encodes a reporter gene introduced in place of a viral gene not essential for replication culture that serves as a marker for viral replication and can be analyzed in a simple and rapid manner. Thus, the present invention allows for the establishment of high throughput screens for anti-viral compounds that include all viral targets required for replication in culture.

As discussed in the Background of the Invention section of the present specification (pages 2-3), single-cycle infectious HIV-1 reporter viruses encoding luciferase as the reporter gene have been described, but steps post-HIV gene expression in an infected cell, such as HIV protease mediated processing of viral precursor polypeptides required for virion maturation, are not easily measured using such reporter viruses. Thus, such viruses are not useful for testing for possible late stage replication inhibitors. Also, replication-competent HIV-1 reporter viruses are known, but are not useful for high volume anti-viral assays because the reporter gene products they encode,

such as CAT, cannot be measured by simple and rapid assays. Haseltine discloses an example of such a virus.

The claims have been amended to clarify that the inventive vectors are suitable for use in high volume anti-viral assays. Haseltine merely discloses a replication competent HIV-1 reporter assay encoding CAT, which, as stated above, is not useful in high volume anti-viral assays, Therefore, Applicants respectfully submit that Haseltine is not a proper reference under Section 102(b).

Moreover, Applicants point out that previous attempts to modify HIV-1 proviral clones with a reporter gene failed to produce replication competent reporter viruses. For example, as set forth in the present specification, the JRFNFLuc virus, which encodes a firefly luciferase gene, was constructed in a manner similar to that set forth in Chen et al. (J. Virol. (1994) 68:654-660) ("Chen"). As set forth at page 17 of the present specification, this virus failed to produce firefly luciferase after the third day of infection, indicating that mature virus core particles were not made and that the virus was not replication competent. Accordingly, at the time of the present invention, the art failed to teach or suggest the replication competent reporter viruses of the present invention which are useful in high throughput assays.

As neither Haseltine nor any other reference provides the requisite teaching to solve the problems which existed in the art at the time of the present invention, Applicants respectfully submit that withdrawal of the rejection under Section 102 is appropriate and is, therefore, respectfully requested.

Section 103 Rejections

The Examiner has rejected Claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over Haseltine, as applied to claims 1, 2, 4, 10 and 11 and Shi.

For the reasons set forth above, Applicants respectfully submit that Haseltine merely sets forth known replication-competent HIV-1 reporter viruses which are not suitable for use in a high throughput screening assay. As such, Shi, which merely discloses the proviral clone HIV-1 Lai and uses MT-2 to grow the virus, cannot remedy the deficiencies of Haseltine.

The Examiner has rejected claims 3, 13-15, 21 and 22 under 35 U.S.C. 103(a) as being unpatentable over Haseltine, as applied to claims 1, 2, 4, 10, 11 and Liu. The Examiner acknowledges that Haseltine does not disclose luciferase or SEAP, but states that Liu teaches that SEAP and Renilla luciferase are useful markers and reporter genes, and therefore it would have been obvious to use a reporter of Liu in the HIV-1 virus of Haseltine.

The Examiner fails to set forth any motivation to use a reporter of Liu in the virus of Haseltine. In fact, the art teaches away from such a combination. As discussed in the present

specification and above, the virus of Haseltine is not suitable for use in a high throughput screening assay due, for example, to the limitations of the reporter used. Haseltine does not suggest any manner of remedying these problems and provides no teaching as to how one skilled in the art would modify the HIV-1 virus of Haseltine to arrive at the present invention. Merely pointing out that the reporter used in the present invention was known in the art, as the Examiner has done by citing Lui, does not remedy this deficiency. Moreover, as stated above, Chen is an example of a luciferase reporter which failed to result in a replication competent HIV-1 virus. As such, this is evidence that merely suggesting that a particular luciferase reporter may be used in a HIV-1 virus does not provide the necessary teaching to arrive at the present invention.

The Examiner has rejected claims 5, 6, 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Haseltine, as applied to claims 1, 2, 4, 10, 11 and Gibbs. The Examiner alleges that Haseltine teaches a replication competent HIV-1 virus with a non-essential region of the virus replaced and a heterologous DNA inserted as a reporter gene to trace HIV infection or monitor the effects of anti-HIV drugs in a screening assay. The Examiner acknowledges that Haseltine does not teach clone pNL4-3 or deletion of some or all vpr, but states that Gibbs teaches proviral clone pN4-3 and that vpr is a non-essential region.

For the reasons set forth above, Applicants respectfully submit that Haseltine merely sets forth known replication-competent HIV-1 reporter viruses which are not suitable for use in a high throughput screening assay. As such, Gibbs, which discloses proviral clone pN4-3 and that vpr is a non-essential region, cannot remedy the deficiencies of Haseltine.

The Examiner has rejected claims 7, 8, 18-20 and 23 under 35 U.S.C. 103(a) as being unpatentable over Haseltine and Liu, as applied to claims 3, 13-15, 21 and 22. The Examiner alleges that Haseltine teaches a replication competent HIV-1 virus with a non-essential region of the virus replaced and a heterologous DNA inserted as a reporter gene to trace HIV infection or monitor the effects of anti-HIV drugs in a screening assay. The Examiner acknowledges that Haseltine does not teach proviral clone of pYU-2, but states that Collman teaches an infection clone of HIV-1, p89.6 which has a novel tropism, Li teaches an infectious proviral clone of pYU-2 and Shi teaches the proviral clone of HIV-Lai and the use of MT-2 cells to grow virus. The Examiner alleges that one skilled in the art would know that the provirus of Collman or Li or Shi could be used in the place of Haseltine.

For the reasons set forth above, Applicants respectfully submit that Haseltine merely sets forth known replication-competent HIV-1 reporter viruses which are not suitable for use in a high throughput screening assay. As such, none of Collman, Li or Shi, each of which discloses a various provirus, can remedy the deficiencies of Haseltine.

Accordingly, Applicants submit that the withdrawal of the rejections under Section 103 is appropriate and is, therefore, respectfully requested.

Applicants respectfully submit that the claims are in condition for allowance. Please direct any questions concerning this Response or any aspect of this case to the undersigned attorney.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Respectfully submitted,

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Date: June 23, 2003

Appendix A

AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A vector that encodes a replication competent HIV-1 virus, said vector comprising an HIV-1 genome in which a region non-essential for viral replication has been replaced by a reporter gene, wherein said vector is suitable for use in a high volume anti-viral assay.

2. (Amended) The vector according to claim 1, wherein said reporter gene is selected from the group consisting of the renilla luciferase reporter gene, the SEAP reporter gene[, the CAT gene,] and the green fluorescence protein gene.

13. (Amended) A vector that encodes a replication competent HIV-1 virus, said vector comprising an HIV-1 genome in which a region non-essential for viral replication has been replaced by a nucleic acid sequence encoding a functional renilla luciferase enzyme, wherein said vector is suitable for use in a high volume anti-viral assay.